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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/547,999	09/07/2006	Daniel Portnoy	B01-050 (BERK-017CIP)	6366
84220	7590	05/13/2009		
UC Berkeley - OTL Bozicevic, Field & Francis LLP 1900 University Avenue, Suite 200 East Palo Alto, CA 94303			EXAMINER DUFFY, PATRICIA ANN	
			ART UNIT	PAPER NUMBER
			1645	
			MAIL DATE	DELIVERY MODE
			05/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/547,999	Applicant(s) PORTNOY ET AL.	
	Examiner Patricia A. Duffy	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14, 15, 25, 26 and 28-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14, 15, 25, 26 and 28-32 is/are rejected.
- 7) ☒ Claim(s) 33 and 34 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-12-09 has been entered.

Claims 14, 15, 25, 26 and 28-34 are pending and under examination.

Rejections Maintained

Claim 14, 15, 25, 26 and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel et al (US Patent No. 6,099,848, issued August 8, 2000) in view of Frazao et al (WO 99/07861, published 18 February 1999) and Loessner et al (Molecular Microbiology, 35(2):324-340, 2000) is maintained for all reasons made of record.

Applicant's arguments have been carefully considered but are not persuasive. Applicants argue that there is no motivation and no expectation of success. This is again not persuasive the record indicates specific motivation and the art provides a reasonable expectation of success in view of the separation of the mycobacterial phage attachment sites from the corresponding mycobacterial phages. Applicants argue that the combination must predict success. This is not the correct legal standard. The art must only provide a reasonable expectation of success not an absolute expectation/prediction of success as argued by Applicants. Applicants reiterate previous arguments that were not persuasive for reasons set forth in the final rejection of 10-15-08. Applicants argue that there is no reason for the skilled artisan to go to the more complicated two vector system. This is not persuasive because the two vector system was shown to be effective for producing an antigen and motivation for other Genera including *Listeria* was specifically articulated by the authors. Furthermore, the instant claims clearly encompass a two vector system and do not exclude the two vector system of the art. Applicants argue that

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the references would require going to the two vector system and going to the untried and and tested Listeriophage A118 integrate and attachment sites. Again, the skill in this art is very high and molecular biological techniques are largely cookbook at the time that this invention was made. The elements were known and the substitution of one functional equivalent for another would be a matter of routine and was suggested by the art. The fact that the art does not indicate a reason for going from homologous to site specific attachment for a *Listeria* vector is not in fact true. The art of Frazao et al explicitly directs one to similar vectors for *Listeria* spp. It does direct one to site-specific integration vectors. That the modification of the art leads on to an alleged more complicated two vector system is again not persuasive because the claims do not exclude a two vector system. Applicant's amendment of the claims to recite "capable of integrase mediated site specific" does not resolve the issue because the site specificity and integrase mediated is defined by the listeriophage attachment site in the integration vector. Therefore, any vector having the listeriophage attachment site would be "capable of integrase-mediated site specific integration". Applicants argue that there is no credible reason to combine the elements and one would not be inherently motivated to do so. This is again not persuasive because credibility and inherency of motivation are not the proper standard for obviousness under 35 USC 103. The examiner has properly shifted the burden and these arguments of counsel do not obviate the rejection of record. Further, *In re Fine*, 837 F.2d 1071, 1075, 5U.S.P.Q.2d 1959 (Fed. Cir. 1988) states that under section 103 a *prima facie* case of obviousness can be established by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art can lead the individual to combine the references. See also *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Furthermore, the courts have held "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146

USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). Finally, an obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). Here we have a substitution of functional equivalents to yield a new combination of known elements, yielding predictable results of an integration vector capable of site specific integration. In the instant case the Office has provided both motivation as per the teaching suggestion and motivation test and also the test for the combination of known elements according to known molecular biological methods because it yielded the predicted result. Applicants again argue that there is no reason to go from homologous to site specific in the record and assert that homologous recombination is different from site specific recombination. This is again not persuasive because the reason is the collective teachings of the references (Frankel et al) indicate that site specific or site directed insertion of DNA encoding the heterologous antigen minimizes the possibility of disruption of other areas of the *Listeria* chromomome which may be essential for growth. One skilled in the art would readily appreciate this teaching and reach to other site-specific means for the same reason. The skilled artisan again would readily appreciate that site specific integration as per the means of Frazao would also meet the desire to have site specific insertion to minimize the possibility of disruption of the genome which may be essential for growth. So the fact that integrase-mediated site-specific recombination is mechanistically different from homologous site-

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specific recombination is irrelevant because the skilled artisan would reach for other site-specific recombination means as directed by the art as combined (see Office Action of 4-3-08) and as a design choice. Applicants argue Shen et al and what the art teaches at the time. This is not persuasive because Shen et al is not a reference in the 103 and is not specifically mentioned by the references as combined and Applicants conclusions are merely speculative in nature. Applicants argue that the amendments to the claims obviate the homologous recombination vector of Frankel et al is not persuasive for the reasons made of record. This is also not persuasive because the motivation statement in the Office Action of 4-3-08 states:

"It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made modify the pAV1 of Frazao et al by substituting the integrase gene and attP site of the A118 bacteriophage of *Listeria monocytogenes* according to Loessner et al for the attachment site region (attP) and the integrase gene of the mycobacteriophage Ms6 of the pAV1 of Frazao et al and transduce attenuated *Listeria* of Frankel with the modified vector of Frazao and Loessner et al for the production of heterologous antigens in vivo by administering the site specific modified attenuated *Listeria* spp expressing a heterologous antigen for the generation of a cellular immune response to antigen because Frazao et al teach that exogenous DNA can be linked to this region to provide for site-specific integration into the genome and that Frazao et al teach that the integrative vectors and the integrating process described is not restricted to mycobacteria and is specifically applicable to other bacteria such as *Listeria* spp. (page 7, first full paragraph) and Frankel et al teach that the preferred method for producing a recombinant *Listeria* having a gene encoding a heterologous antigen integrated into the chromosome thereof and that the vaccine expressing the integrated heterologous antigen can be administered to an animal so as to provide for a cellular immune response."

The modification is of the pAV1 vector of Frazao et al, not the vector of Frenkel et al. Applicants are reminded that it is the combination of references that render the claims obvious. The Office has relied upon particular teachings of specific references and Applicants continue to argue the non-relied upon teachings that are not specifically articulated in the obviousness statement of record. Applicants argue that one skilled in

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the art would need a working example of the Listerophage attachment sites to imply that an actual reduction to practice must occur before the skilled artisan can have any expectation of success. This is not persuasive because the skill in this art is particularly high and molecular biology routine at the time of the invention. This is also not persuasive because the art articulates an expectation of success by specifically directing the skilled artisan to *Listeria*. The fact that the art merely exemplifies *M. tuberculosis* and associated bacteriophage as a functional bacteriophage/host pair that can have the att site removed and function make to a site-specific integrase mediated vector does not provide a lack of expectation of success for the other suggested bacteriophage/host systems. In contrast, the functionality of the removal of the att site of a bacteriophage provides for a reasonable expectation of success. In view of the high skill in this art, the routine nature of molecular biology at the time the invention was made and the fact that cited art itself provides for a reasonable expectation of success by exemplification of the mycobacteriophage M6 elements and a mycobacterium, the rejection is maintained.

Status of Claims

Claims 14, 15, 25, 26 and 28-34 stand rejected. Claims 33 and 34 are objected to as depending from the rejected independent claim.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 7:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisors, Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Primary Examiner